

**REMARKS**

Entry of the foregoing, reexamination and reconsideration of the subject matter identified in caption, pursuant to and consistent with 37 C.F.R. § 1.112 and in light of the remarks which follow are respectfully requested.

Claims 12-32 are pending in the application.

By the above amendment, claim 15 has been amended to correct a typographical error. Clearly, this amendment does not constitute a narrowing amendment since it merely corrects a typographical error.

Applicant thanks the Examiner for withdrawing the rejection of the claims over *Apfel et al.* (J. Biol. Chem. (1995), 270 (51), 30765-72) upon consideration of Applicant's arguments presented in the Request for Reconsideration filed on June 22, 2001. In view of the above amendment and the following remarks, Applicant submits that all of the outstanding rejections should be withdrawn.

Turning now to the Official Action, claims 12-13 and 19-23 stand rejected under 35 U.S.C. § 102(b) as being anticipated by *Obushak, M.D. et al.* (DN 113:152173, HCAPLUS; Abstract of Zh. Org. Khim. (1990), 26 (4), 873-80) or Krutosikova, A. et al. (DN 84:58390, HCAPLUS; abstract of Collect. Czech., Chem. Commun. (1975), 40(11), 3362-9). For at least all of the reasons that follow, withdrawal of these rejections is in order.

The present invention relates to bicyclic aromatic compounds as novel and useful industrial products. The present invention further relates to the use of these novel

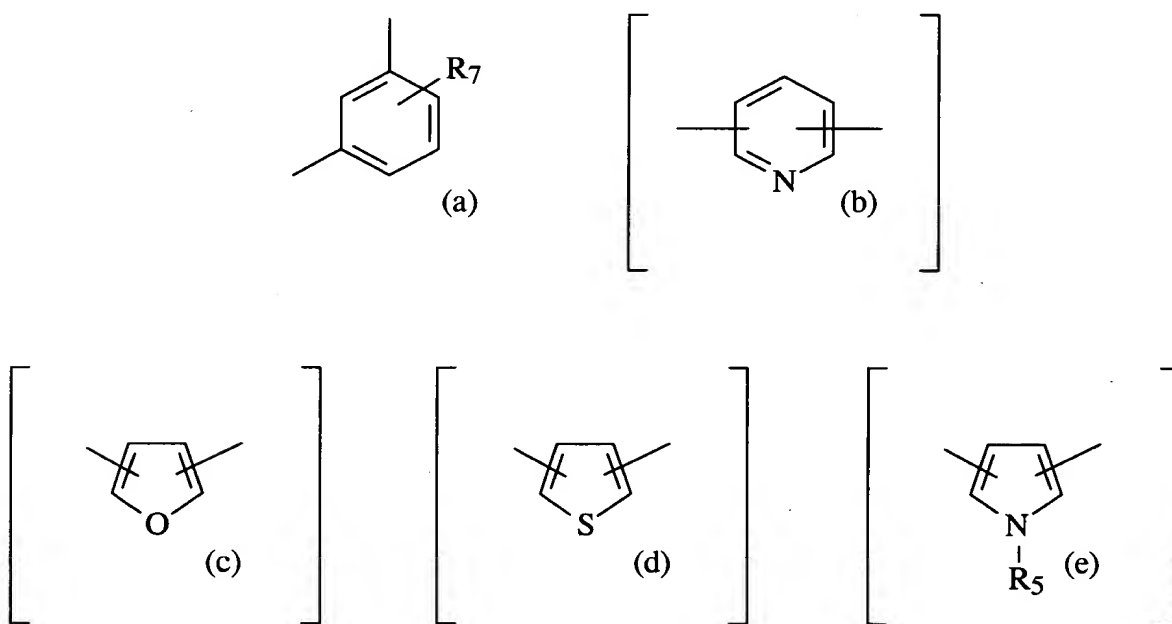
compounds in pharmaceutical compositions intended for use in human or veterinary medicine, or alternatively in cosmetic compositions. See specification at page 1, lines 2-7.

For example, independent claim 12 sets forth a bicyclic aromatic compound having the general formula (I):

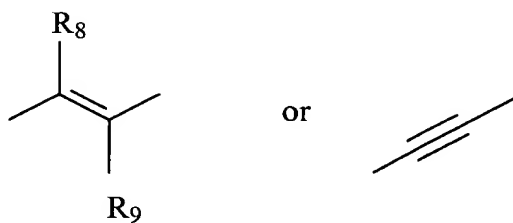
wherein,

-  $R_1$  represents (i) the  $-CH_3$  radical, (ii) the radical  $-CH_2OR_5$ , or (iii) the radical  $-COR_6$

- Ar is a radical of a formula selected from formulae (a) - (e):



- X represents



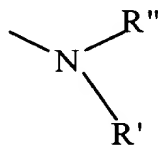
-  $R_2$  and  $R_3$ , which may be identical or different, represent

(i) a hydrogen atom, (ii) an alkyl radical having at least 3 carbon atoms, among which the carbon attached to the phenyl radical is substituted with at least two carbon atoms, (iii) a radical  $-OR_5$ , (iv) a radical  $-SR_5$ , with the proviso that  $R_2$  and  $R_3$ , taken together, may form with the adjacent aromatic ring a 5- or 6-membered ring optionally substituted with methyl groups and/or optionally interrupted by an oxygen or sulphur atom, with the further proviso that  $R_2$  and  $R_3$  cannot at the same time have the meanings (i), (iii) and (iv),

-  $R_4$  and  $R_7$ , which may be identical or different, represent a hydrogen atom, a halogen atom, a linear or branched alkyl radical having from 1 to 20 carbon atoms or a radical  $-OR_5$ ,

-  $R_5$  represents a hydrogen atom, a lower alkyl radical or a radical  $-COR_{10}$

-  $R_6$  represents: (a) a hydrogen atom, (b) a lower alkyl radical, (c) a radical of formula:



or (d) a radical  $-OR_{11}$

-  $R_8$  and  $R_9$ , which may be identical or different, represent a hydrogen atom or a lower alkyl radical,

-  $R_{10}$  represents a lower alkyl radical,

-  $R_{11}$  represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 20 carbon atoms, and alkenyl radical, a mono- or polyhydroxyalkyl radical, an optionally substituted aryl or aralkyl radical, a sugar residue or an amino acid or peptide residue,

-  $R'$  and  $R''$ , which may be identical or different, represent a hydrogen atom, a lower alkyl radical, a mono- or polyhydroxyalkyl radical, an optionally substituted aryl radical or an amino acid or sugar residue, or alternatively, taken together form a heterocycle,

a salt thereof or an optical or geometrical isomer thereof.

Accordingly, the compound defined in claim 1 specifies that  $R_2$  and  $R_3$  can be a radical (i), (ii), (iii) or (iv). Claim 1 provides the further proviso that  $R_2$  and  $R_3$  cannot at the same time be (i), (iii) and (iv). Thus, the following combinations are specifically disclaimed under the definition of claim 1: (a)  $R_2 = R_3 = (i)$ ; (b)  $R_2 = R_3 = (iii)$ ; (c)  $R_2 = R_3 = (iv)$ ; (d)  $R_2 = (i) + R_3 = (iii)$  or  $R_3 = (iv)$ ; (e)  $R_2 = (iii) + R_3 = (i)$  or  $R_3 = (iv)$  or (f)  $R_2 = (iv) + R_3 = (iii)$  or  $R_3 = (i)$ .

The Abstract of *Obushak* and the Abstract of *Krutosikova* disclose compounds wherein  $R_2 = H$  and  $R_3 = O-Me$  and wherein  $R_2 = O-Me$  and  $R_3 = H$ , respectively. As explained above, these combinations are specifically disclaimed from claim 1.

Accordingly, the Abstract of *Obushak* and the Abstract of *Krutosikova* clearly fail to disclose each and every element of the presently claimed invention.

For at least these reasons, the claimed invention is not anticipated by *Obushak* or *Krutosikova*. Accordingly, withdrawal of the § 102(b) rejections based on *Obushak* and *Krutosikova* is respectfully requested.

Claims 16-18 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not adequately described in the specification. For at least all of the reasons that follow, withdrawal of the rejection is in order.

The Official Action alleges that no drug is broadly effective against all forms of cancer and that the claims should accordingly be limited to certain types of cancer supported in the specification. Applicant respectfully disagrees. More specifically, Applicant submits that retinoid compounds are generally effective against cellular differentiation and proliferation mechanisms. See, for example, "THE RETINOIDS: Biology, Chemistry, and Medicine," (Second Edition, edited by M.B. Sporn, A.B. Roberts, and D.S. Goodman, Raven Press, Ltd., New York, 1994). For example, in chapter 15 entitled "Retinoids and Human Cancer," the above publication states:

"The scientific basis for the use of retinoids as preventive and therapeutic agents in human cancer is discussed in detail in this book. The capacity of retinoids to modulate the differentiation and proliferation of both preneoplastic and neoplastic cells is an important biologic property of the substances (Lotan, 1980)... ."

Clearly, because cellular differentiation and proliferation mechanisms occur in numerous disorders and are not limited to cancer, retinoids are useful in treating numerous disorders. Additionally, it is well known that retinoids can be useful in treating cancers, see, for example, Fitzpatrick's, DERMATOLOGY IN GENERAL MEDICINE, 5<sup>th</sup> Edition, Chapter 256, Page 2810, which states:

"Retinoids have diverse biological effects. They effect cell growth and differentiation, morphogenesis, inhibition of tumor promotion and malignant cell growth, immunomodulatory actions, and alterations in cellular cohesiveness." "In the treatment of cancer, retinoids are also useful due to their antiproliferative/pro-differentiating effects on cancer cells."

Clearly, the above document by Fitzpatrick discloses that there is a strong interest in retinoid compounds because of the effect these compounds have on cellular mechanisms notably linked to cancer development. More importantly, the disclosure of Fitzpatrick clearly indicates that retinoids are generally effective in cancer treatment and are not limited to effective treatment of specific types of cancer. Further, the compound of the presently claimed invention defines novel retinoid compounds that exhibit effects on cellular differentiation and proliferation. Accordingly, Applicant submits that the novel retinoid compounds of the presently claimed invention can be used to treat numerous disorders involving cellular differentiation and proliferation and are not specifically limited to being effective in treating only specific types of cancer.

For at least these reasons, withdrawal of the § 112, first paragraph, rejections is respectfully requested.

Claim 28 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. For at least the reasons that follow, withdrawal of the rejection is in order.

As explained in the specification at page 3, lines 9-13,  $R_2$  and  $R_3$  taken together can form with the adjacent aromatic ring a 5- or 6-membered ring optionally substituted with methyl groups and/or optionally interrupted by an oxygen or sulfur atom. Accordingly, Applicant submits that claim 28 would be readily understood by one of ordinary skill in the art, when considered in view of the specification, to mean that  $R_2$  and  $R_3$ , taken together,

can form with the adjacent aromatic ring that is optionally substituted with methyl groups and/or optionally interrupted by an oxygen or sulfur atom.

For at least these reasons, withdrawal of the § 112, second paragraph, rejection is respectfully requested.

Claims 14-15, 24-27 and 29-32 stand objected to as being directed to non-elected subject matter. In response, Applicant submits that upon notification that the application is otherwise in condition for allowance, Applicant will authorize cancellation of any non-elected subject matter.

Claim 15 stands objected to for including a spelling error. Applicant has amended claim 15 to obviate this objection. Accordingly reconsideration and withdrawal of the objection are respectfully requested.

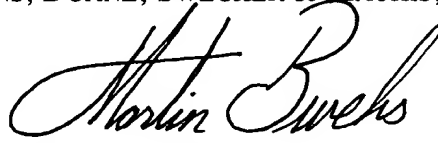
From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

If there are any questions concerning this paper or the application in general, the Examiner is invited to telephone the undersigned at the Examiner's earliest convenience.

Respectfully submitted,

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